

Clinical characteristics of children with multisystemic inflammatory syndrome associated with COVID-19

Clinical characteristics of MIS-C associated with COVID-19

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Abstract

Aim: Coronavirus disease 2019 (COVID-19) has become a public health threat to people all over the world in 2020 and 2021. The Centers for Disease Control and Prevention (CDC) and WHO (World Health Organization) have named a novel disease multisystem inflammatory syndrome in children (MIS-C). Herein we aimed to present a group of pediatric patients with MIS-C, who were followed up in our clinic.

Material and Methods: We retrospectively reviewed the medical records of patients who were followed up at our University Hospital with the diagnosis of MIS-C between January 2021 and May 2021.

Results: The mean age of 9 patients was 87.4 ±17.8 years (range 6-161 months); six of the patients were male. All patients had fever at admission. The duration of the fever was between 3 and 7 days. Four patients (44.4%) had terminal ileitis on ultrasonic examination. The laboratory tests of the patients revealed leukocytosis in 4 (44.4%) patients, anemia in 5 (55.5%) patients, thrombocytopenia in 1 (11.1%) patient, and a high CRP level in 8 (88.8%) patients. All patients had high sedimentation rates and procalcitonin levels. One (11.1%) patient was operated on for terminal ileitis. All patients were treated with steroids (1-2 mg/kg prednisolone) and IVIG (2gr/kg). Patients who needed ICU admission were also treated with vasoactive drug infusion (intravenous dopamine).

Discussion: There is a need for increased awareness among pediatricians that MIS-C should come to mind, especially in patients with long-lasting fever and signs and symptoms that resemble Kawasaki disease.

Keywords

Multisystem Inflammatory Syndrome, Children, Hyperinflammation, Steroid, Intensive Care, COVID-19

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Introduction

Coronavirus disease 2019 (COVID-19) has become a public health threat to people all over the world in 2020 and 2021. The lower airway tract is the primary target of the infection [1]. Acute respiratory distress syndrome (ARDS), septic shock, and coagulation disorders are severe complications of this infection, which are rare in children [2]. Children constitute about 1% of all COVID-19 cases in Turkey. COVID-19 has a milder clinical course in children than in adults [3]. Previous reports have shown that the incidence of hyper-inflammation in children is relatively low in comparison to adults [4]. However, Riphagen S. et al. [5] reported several pediatric cases with previous COVID-19 who suffered systemic symptoms that resemble Kawasaki disease (KD) (World Health Organization. Multisystem Inflammatory Syndrome in Children and Adolescents with COVID-19: Scientific Brief, 15 May 2020) . Afterward, a lot of similar cases have been reported from around the world. The Centers for Disease Control and Prevention (CDC) and WHO (World Health Organization) named this novel disease multisystem inflammatory syndrome in children (MIS-C), which differs in clinical presentation from KD, Toxic shock syndrome (TSS), and Macrophage activation syndrome (MAS)/Hemophagocytic lymphohistiocytosis (HLH) [6] (Centers for Disease Control and Prevention. Manage Anxiety & Stress. Atlanta, GA; 2020). Herein we present a group of pediatric patients with MIS-C, who were followed up in our clinic. We evaluated and compared the clinical characteristics of these patients.

Material and Methods

We retrospectively reviewed the medical records of patients who were followed up at our university hospital with the diagnosis of MIS-C between January 2021 and May 2021. Children who were diagnosed with severe COVID-19 disease and met the criteria for MIS-C provided by WHO and CDC were included in the study (World Health Organization. Multisystem Inflammatory Syndrome in Children and Adolescents with COVID-19: Scientific Brief, 15 May 2020). Patient data, including demographic characteristics, medical history, symptoms, signs, laboratory findings, and outcomes, were collected from the patients'

medical records. Written informed consent was obtained from their parents. The inclusion criteria required proof of COVID-19 exposure confirmed by PCR (polymerase chain reaction) analysis, antigen test, and/or serology. Suspected cases with a positive PCR result or serum-specific antibodies against SARS-CoV-2 were considered confirmed cases [7].

Statistical Analysis

We reported the categorical variables as frequency rate and percentage and continuous variables as mean and standard deviation (SD). All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 20.0 software (SPSS Inc.)

Ethics committee approval for the study was obtained from the Clinical Research Ethics Committee of XXX University (Date: 30.06.2021 / Decision no:2021.06.21)

Results

The mean age of the 9 patients was 87.4 ± 17.8 months (range 6-161 months); six of the patients were male. Seven patients had a history of contact with a COVID-19 positive person. The diagnosis of COVID-19 was made by PCR in 2 patients, by serology in 4 patients, and by antigen test in 3 patients. All patients had fever at admission. The duration of the fever was between 3 and 7 days. Six (66.6%) patients had nausea, 5 (55.5%) had abdominal pain, 5 (55.5%) had a rash, 3 (33.3%) had a headache, 7 (77.7%) had somnolence, 3 (33.3%) had conjunctivitis, 1 (11.1%) had arthritis/arthralgia, and 6 (66.6%) had hypotension. Four patients (44.4%) had terminal ileitis on ultrasonic examination.

The laboratory tests of the patients revealed leukocytosis in 4 (44.4%) patients, lymphopenia in 3 (33.3%) patients, anemia in 5 (55.5%) patients, thrombocytopenia in 1 (11.1%) patient, a high CRP level in 8 (88.8%) patients, and a moderate CRP elevation in 1 (11.1%) patient. All patients had high sedimentation rates and procalcitonin levels. Seven (77.7%) patients had high fibrinogen levels. The Pro-BNP levels of 7 patients were above normal ($n > 350$ pg/ml), with two of them had considerably high levels (7488 and 3590 pg/ml) (Table). One (11.1%) patient was operated on for terminal ileitis. Three patients needed intensive

Table 1. Clinical and laboratory parameters of the patients with MIS-C

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age (months)	6	161	135	116	124	93	70	71	11
Diagnostic method	AgT ¹	AgT	S*	S*	S*	PCR ²	PCR	S*	AgT
The Duration between COVID-19 and presentation (month)	1	1	3	1	1	1	1	1	3
Gender	M	M	F	F	F	M	M	M	M
Extra clinical diagnosis	Hemiparesis		Operated ileit	Convulsion	NCL ³	NCL ³	NCL ³		
⁴ CRP (mg/L) (admission/follow up) (N<5)	85/0.3	219/100	134/42	6	146/51	202/2	61	108	71/3
⁵ ProBNP (pg/ml)(admission) (350<N)	450	7488	487		3590	500	560		400
Steroid	+	+	+	+	+	+	+	+	+
⁶ IVIIG	+	+	+	+	+	+	-	+	?
Vasoactive infusion (Dopamine)	-	+	-	+	-	-	+	+	-
Duration of Hospitalization	9	9	6	20	7	22	13	10	5
Result	Recovered	Recovered	Recovered	ICU ⁷ - Recovered	Recovered	Recovered	ICU ⁸	ICU ⁹ Recovered	Recovered

Abbreviations; ¹AgT: Antigene test, *S: Serology (SARS-Cov-2 IgG serology), ²PCR: Polymerase chain reaction, ³NCL: Neuronal ceroid lipofuscinosis, ⁴CRP: C-reactive protein
⁵ProBNP: B Type Natriuretic Peptide, ⁶IVIIG: Intravenous immune globulin, ⁷ICU: Intensive care unit

care unit admission. Two of them were siblings (M/M), both had metabolic disease, namely neuronal ceroid lipofuscinosis type 1, and both had respiratory distress. One of these patients died of multiorgan failure and the other was intubated. Both of them had the highest procalcitonin (5.4 and 4.4 ng/ml) and the lowest albumin levels (2.5 and 2.6 gr/dl) in the whole study group. The deceased patient had the highest D-Dimer level. The third patient, a 116-month-old female, needed ICU admission due to convulsion and thrombocytopenia. None of these three patients had conjunctivitis. All of patients had hypotension. None of the patients, except for the deceased patient, developed acute kidney failure or liver failure.

All patients were treated with steroids (1-2 mg/kg prednisolone) and IVIG (2gr/kg). Patients who needed ICU admission were also treated with vasoactive drug infusion (intravenous dopamine).

Discussion

The experience with COVID-19 during this pandemic has shown that symptoms are less severe in children than in adults [8]. In the present study, we reported clinical manifestations of 9 Turkish children with MIS-C, whose PCR/Serology/Antigen test was positive for COVID-19. The incidence of MIS-C was reported as 2 per 100,000 persons below 21 years of age [9]. We should emphasize that children may still develop MIS-C despite an asymptomatic COVID-19 course [10].

All patients had a persistent fever that was one of the main characteristics of MIS-C. A previous report [11] found that conjunctivitis and rash were also the significantly distinctive features of MIS-C. This report suggested that if conjunctivitis is supported by higher acute phase reactants, the diagnosis of MIS-C seems likely.

In our patients, elevated levels of acute-phase reactants, namely CRP, sedimentation rate, fibrinogen, or procalcitonin were noteworthy. Although fever, conjunctivitis, rash, and elevated acute phase reactants remind us of Kawasaki disease [12,13], abdominal pain and signs of terminal ileitis were the distinguishing findings in our MIS-C patients. Moreover, proof of previous COVID-19 disease confirms the diagnosis of MIS-C. Cardiac injury associated with COVID-19 infection has been described in the adult population [14]. Some case series have shown left ventricular dysfunction in MIS-C [15,16]. Myocardial dysfunction diagnosed by ECHO and/or increased troponin-I or pro-BNP levels has been reported in 51-90% of patients with MIS-C [16-18]. Only the deceased patient had congestive heart failure, whereas the rest of the patients had normal echocardiographic findings. However, the Pro-BNP levels of seven patients were above normal, with two of them having had considerably high levels. These two patients recovered. Therefore, we suggest that the Pro-BNP level may not be a prognostic factor. We also suggest that the mechanism of cardiac failure is not associated with myocardial damage associated with acute SARS-CoV-2 infection. Cardiac features overlapped with toxic shock syndrome together with cardiac inflammation (MIS-C).

In a previous study [19], 83.3% of patients had GI involvement. Among them, five patients had severe GI manifestations presenting with appendicitis in three of them, and pancreatitis in two patients. Studies have shown that ACE2 receptors are

abundant in the GI tract [17]. These findings supported the high prevalence of GI involvement in patients with MIS-C. Six (66.6%) of our patients had nausea/vomiting. Five (55.5%) of them had abdominal pain and 4 of these patients also had terminal ileitis on USG. Three of these patients were female, which was a noteworthy point.

The neurotropic and neuro-invasive potentials of coronaviruses have been reported previously. However, the absence of the virus in the cerebrospinal fluid in COVID-19 patients supports the existence of other factors. Researchers suggest that cellular edema of neurons due to inflammatory response and immune-mediated neuronal damage may be the reason for the neurological manifestations in children with MIS-C [20]. In our study, none of the children manifested severe neurological signs and symptoms, but 7 patients had somnolence.

The American College of Rheumatology (ACR) issued a clinical guideline for the management of MIS-C [21], since hyperinflammation is a common process in MIS-C according to this guideline, IVIG and/or glucocorticoids are recommended as first-line treatments. Thus, we started steroids and IVIG in all patients. During the follow-up period, 6 patients recovered completely with this treatment.

Conclusion

Although MIS-C is a rare clinical entity, it appears to be highly fatal. Therefore, it is urgent to diagnose the condition and start appropriate treatment. Hence, there is a need for increased awareness among pediatricians that MIS-C should come to mind, especially in patients with long-lasting fever and signs and symptoms that resemble KD.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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